Mechanisms to protect hESC-derived cells from allogenic immune rejection

Grant Award Details

Mechanisms to protect hESC-derived cells from allogenic immune rejection

Grant Type: Basic Biology IV

Grant Number: RB4-06244

Project Objective: Goal of the project is to develop molecular strategies to protect hESC-derived cells and tissues from immune rejection in allogeneic hosts. The focus of this application is defining and characterizing the mechanism(s) of allogenic immune response suppression to hESC and hESC derived cells modified with potent inhibitory receptors expressed by T cells.

Investigator:

Name:	Ananda Goldrath
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,160,997

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Mechanisms to protect hESC-derived cells from allogenic immune rejection
Public Abstract:	The potential of human embryonic stem cells (hESC) to differentiate into a tremendous range of biologically active cells/tissues is the basis for many novel therapeutic strategies. However, immune-mediated rejection of hESC-derived tissues by the patient remains a significant barrier to the promise of regenerative therapies. Therefore, it is key to develop strategies to induce immunological tolerance to hESC-derived tissues/cells, thereby inhibiting rejection and evading the risks of routinely used systemic immunosuppressants, including the cytotoxicity and increased risk of infection and cancer. To accomplish this objective, we have expressed proteins known to restrain lymphocyte activity in hESC-derived cells. Importantly, when transplanted into mouse models with functional human immune system, we find that transplanted cells derived from modified hESCs evade rejection and induce sustained immunological tolerance. This is the first time the immune responses to hESC-derived cells have been studied in an in vivo context. Here, we propose to explore the molecular pathways and immune cell types that mediate the induction of immune tolerance and pursue additional targets for further blunting rejection of tissue grafts derived from hESC. To achieve the full potential of hESC-based therapy, it is critical to develop effective approaches to promote long-term immune tolerance of hESC-derived cells, and our studies provide a novel strategy to this end.
Statement of Benefit to California:	Thousands of Californians receive life-saving tissue transplantation each year. However, the human and medical cost of long-term immunosuppression to promote survival of grafted cells and the limited availability of donor tissues/cells prevents the realization of the full benefits. The potential of human embryonic stem cells (hESC) to differentiate into a tremendous range of biologically active cells/tissues is the basis for many novel therapeutic strategies. However, immune-mediated rejection of hESC-derived tissues remains a significant barrier to the promise of regenerative therapies. Thus, it is key to develop strategies to induce immunological tolerance to hESC-derived tissues/cells, which will allow the clinic realization of the full range of benefits to the health of Californians. We propose a novel approach to promote long-term acceptance of hESC-derived tissues and to better understand the mechanisms of immune tolerance in the context of tissue transplantation. We will focus on the immune tolerance of hESC-derived lung epithelial cells that have been shown to rescue lung functions in animal models, as this cell therapy will save the life of patients with various lung diseases such as the chronic obstructive lung diseases that are major killers in California and pose tremendous burden on medical care in our state. Our research will thus lead to important progress in stem cell therapies to better meet the needs of Californians.

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